Northwestern Medicine

Physician FAQs

(For the most up-to-date information regarding COVID-19 treatment options visit **Northwestern Medicine ASP Evidence Review for Inpatient Treatment Options for COVID-19. Available at: https://asp.nm.org/)**

Q: Should ACE-Inhibitors and ARBs be discontinued in patients with COVID-19?
A: There are currently no data or evidence to support the discontinuation of ACE-Inhibitors (ACEIs) or ARBs in patients with COVID-19. Initial concern was raised with ACEIs and ARBs in patients diagnosed with COVID-19 because it binds to target cells through the angiotensin-converting enzyme 2 (ACE2). Epithelial cells of lungs, intestines, kidneys and blood vessels express ACE2. Medications such as ACEIs and ARBs are thought to increase expression of ACE2 through the RAAS system, however there are conflicting findings in animal and human studies. The increase in ACE2, as the host cell entry point, is hypothesized to lead to an increase in transmission of the virus. On the contrary, there is a hypothetical benefit with ACEIs and ARBS. The thought is these agents may have a protective effect against lung damage or interfere with the binding of the virus.

With uncertainty regarding whether ACEI and ARBS are beneficial, harmful, or neutral, physicians and patients are questioning whether patients should hold or continue their ACEI or ARB during the COVID-19 Pandemic. Twelve professional societies, including the joint statement from the Heart Failure Society of America/American College of Cardiology/American Heart Association (HFSA/ACC/AHA), have released statements on the topic. The consensus across all societies is for patients to continue their prescribed ACEI or ARB.

A few studies have investigated the impact of ACEIs/ARBs on the risk of developing COVID-19 and the severity of the disease once infected. A retrospective observational study (Reynolds HR, et al) completed in New York reviewed 12,594 patients with a COVID-19 test result. In patients taking ACEI/ARBs, authors found no substantial increase in the likelihood of testing positive for COVID-19 or experiencing a severe case of COVID-19. In addition, a population-based case-control study (Mancia G, et al) in Italy had 6272 patients with COVID-19 matched to controls by age, sex, and municipality of residence. The authors found there was no association with the use of ACEIs/ARBs with COVID-19 among case patients. A single-center case series (Li J, et al) with 362 hypertensive patients (115 taking ACEIs/ARBs) infected with COVID-19 found there was no difference in disease severity, risk of death, and complications in patients taking ACEIs/ARBs.

Lastly, a retrospective, observational cohort (Zhang P. et al) including 1128 patients with hypertension (188 taking ACEI/ARB and 940 without using ACEI/ARB) diagnosed with COVID-19 in China. In both unmatched and propensity matched cohort regressions with adjustment, the authors observed prior or concurrent use of ACEI or ARB was associated with a significantly lower 28-day all-cause mortality. Given the limitations of retrospective observational designs, there remains a need for randomized, controlled trials. Currently, there are 2 clinical trials underway with losartan (NCT04312009, NCT04311177) in adult patients with COVID-19.

Trusted Resources:

- HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in covid-19. From American College of Cardiology website. Accessed Mar 23 2020. Available from https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19
- Zheng, Y, Ma, Y, Zhang, J, et al. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020. doi: 10.1038/s41569-020-0360-5
- Reynolds, HR, Adhikari S, Pulgarin C. Renin-Angiotensin-Aldosterone System Inhibitors and risk of COVID-19. *N Engl J Med*. 2020 May 1. doi: 10.1056/NEJMoa2008975
- Mancia G, Rea F, Ludergnani M, et al. Renin-Angiotensin-Aldosterone System Blockers and risk of COVID-19. *N Engl J Med*. 2020 May 1. doi: 10.1056/NEJMoa2006923
- Li J, Wang X, Chen K, et al. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *Jama Cardiol*. 2020 Apr 23. doi: 10.1001/jamacardio.2020.1624.
- Zhang P, et al. Association of inpatient use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients with Hypertension Hospitalized With COVID-19. *Circ Res*. 2020 Apr 17. doi: 10.1161/CIRCRESAHA.120.317134. Online ahead of print.
- U.S. National Library of Medicine. ClinicalTrials.gov. Accessed Apr 23 2020. Available from https://clinicaltrials.gov/

Q: When is treatment of COVID-19 with hydroxychloroquine (Plaquenil®) indicated?
A: The use of hydroxychloroquine is no longer recommended for the treatment or prevention of COVID-19 due to lack of benefit and risk of toxicity. In-vitro studies showed that hydroxychloroquine may be effective in the treatment of SARS-CoV-2 infection, but recent clinical trials on humans have shown otherwise. The FDA had issued an emergency use authorization (EUA) for the use of hydroxychloroquine on March 28, 2020 in response to the rapidly spreading pandemic. However, this EUA has been revoked on June 15 due to lack of efficacy in recent clinical trials. Treatment with hydroxychloroquine can increases the patient risk for QT prolongation, dysrhythmia, and death. The associated risks outweigh any potential benefit, therefore it should be avoided.

The National Institutes of Health (NIH) have revised their COVID-19 treatment guidelines to recommend **against** the use of chloroquine or hydroxychloroquine for the treatment of COVID-

19 outside of clinical trials. Also, the guidelines recommend against the use of any agents, including hydroxychloroquine for the prevention of COVID-19. In a randomized clinical trial, hydroxychloroquine failed to demonstrate a significant benefit as post-exposure prophylaxis for COVID-19.

Indiscriminate use of this medication runs the risk of exacerbating limited supplies, which would prevent patients such as those with lupus, where hydroxychloroquine is potentially life-saving, from obtaining the drug.

Trusted Resources:

- Northwestern Medicine ASP Evidence Review for Inpatient Treatment Options for COVID-19. Available at: https://asp.nm.org/
- CDC: Information for Clinicians on Therapeutic Options for COVID-19 Patients: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html
- NIH: COVID-19 Treatment Guidelines: https://www.covid19treatmentguidelines.nih.gov/therapeutic-options-under-investigation/antiviral-therapy/

Q: Is there evidence for use of azithromycin and hydroxychloroquine for COVID-19?
A: At this time, evidence regarding the use of this combination is lacking. The National Institutes of Health (NIH) COVID-19 guidelines recommend against the use of this combination for the treatment of COVID-19.

There are no published randomized clinical trials testing the efficacy of the combination of hydroxychloroquine and azithromycin. In a large cohort study of 1,438 patients in New York State, treatment with hydroxychloroquine and azithromycin did not result in a difference in mortality. A pre-print publication by Gautret and colleagues evaluated the use of the combination of hydroxychloroquine and azithromycin to treat patients infected with the SARS-CoV-2 virus. In this paper, 100% viral clearance occurred in six patients after five to six days of this combination, which was greater than hydroxychloroquine alone (57%). Gautret and colleagues also published a non-peer reviewed paper of 80 patients with similar findings. However, this study has serious flaws in methodology and the findings should be interpreted cautiously. Another research group showed no viral suppression in 11 consecutive patients to whom they administered the combination. Additionally, additive adverse effects on cardiac conduction are concerning, which puts patients at risk of serious, life-threatening arrhythmias. A case series in the US has reported the incidence of QTc prolongation in 84 patients with COVID-19 who were treated with this combination.

Trusted Resources:

- Northwestern Medicine ASP Evidence Review for Inpatient Treatment Options for COVID-19. Available at: https://asp.nm.org/
- Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA. Published online May 11, 2020. doi:10.1001/jama.2020.8630
- Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as atreatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents 2020 (ahead of print)
- Gautret P, Lagier JC, Parola P, et al. Clinical and mirobiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an obeservational study. Pre-preprint 27 March 2020 COVID-IHU-2-1
- Hulme OJ, Wagenmakers EJ, Damkier P, et al. Reply to Gautret et al 2020: A Bayesian reanalysis of the effects of hydroxychloroquine and azithromycin n viral carriage in patients with COVID-19. medRxiv preprint doi: https://doi.org/10.1101/2020.03.31.20048777
- Chorin E, Dai M, Shulman E, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nature Medicine. 2020. Available at: https://doi.org/10.1038/s41591- 020-0888-2.
- Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infections. www.idsociety.org/COVID19guidelines

Q: Is there prophylaxis I should be taking if I am seeing patients with potential COVID-19?
A: There are currently no data or recommendations regarding prophylaxis for COVID-19. Appropriate use of PPE remains the mainstay to prevent transmission.

Trusted Resources:
- Therapeutic Options for Patients with COVID-19, CDC. https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html

Q: When is treatment of COVID-19 with remdesivir indicated?
A: Remdesivir is an investigational antiviral agent originally developed for Ebola virus that has shown activity against SARS-CoV-2. It is now available by clinical trial or by emergency use authorization (EUA). Currently, there is an ongoing clinical trial at Northwestern Memorial Hospital. EUA remdesivir is available at all NM system hospitals. More information regarding these trials is available in the NM ASP Evidence Review Document linked below. For EUA information please visit asp.nm.org for the Remdesivir EUA Fact Sheet for Healthcare Providers.

Trusted Resources:
- Northwestern Medicine ASP Evidence Review for Inpatient Treatment Options for COVID-19. Available at: https://asp.nm.org/

- Clinical Trial: https://www.clinicaltrials.gov/ct2/show/NCT04292899?cond=remdesivir&draw=2&rank=4
- Clinical Trial: https://www.clinicaltrials.gov/ct2/show/NCT04292730?cond=remdesivir&draw=2&rank=5
- Therapeutic Options for Patients with COVID-19, CDC. https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html
- NIH: COVID-19 Treatment Guidelines: https://www.covid19treatmentguidelines.nih.gov/therapeutic-options-under-investigation/antiviral-therapy/

Q: When are Interleukin-6 (IL-6) inhibitors (tocilizumab and sarilumab) indicated in the treatment of COVID-19?

A: The dramatic increase in inflammatory markers accompanied by rapid progression to ARDS in COVID-19 patients may be associated with cytokine storm provoked by the virus. Interleukin-6 (IL-6) inhibitors such as tocilizumab have been used to control cytokine storm in patients who have received CAR-T therapy. Zhang and colleagues published a paper outlining a proposed role for IL-6 inhibitors in severe manifestations of COVID-19. Xu and colleagues published their experience from 20 patients with severe or critical COVID-19 and improvements in biomarkers and discharge from the hospital in 19 out of 20 patients. A number of clinical trials are also underway to examine the role and impact of both tocilizumab and sarilumab dosing and timing on efficacy in COVID-19. At this time, optimal use of these agents is under clinical investigation. Very limited evidence currently suggests a role for critically ill patients with severe COVID-19. The Infectious Diseases Society of America recommends tocilizumab for admitted patients only within the context of a clinical trial. The NIH states there is insufficient evidence to recommend either for or against use of IL-6 inhibitors at this time.

Trusted Resources:

- Northwestern Medicine ASP Evidence Review for Inpatient Treatment Options for COVID-19: Available at: https://asp.nm.org/
- Zhang C, Zhao W, Li JW et al. The cytokine release syndrome(CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce mortality. International Journal of Antimicrobial Agents (2020), doi: https://doi.org/10.1016/j.ijantimicag.2020.105954
- XuX, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. chinaXiv:202003.00026v1
- Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infections. www.idsociety.org/COVID19guidelines
- NIH: COVID-19 Treatment Guidelines: https://www.covid19treatmentguidelines.nih.gov/therapeutic-options-under-investigation/antiviral-therapy/

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Q: Is zinc effective for treating coronavirus (COVID-19) infections?
A: Zinc is an essential trace element that is known to aid in humoral and cell-mediated immunity and has been studied in treating other viral illnesses as well; however, the mechanism of action in viral infections is largely unknown. There are currently no data or evidence to support the use of zinc supplementation in treating patients with COVID-19. There is a hypothetical benefit that zinc may inhibit SARS-CoV2 replication based on previous in vitro data showing zinc can inhibit SARS-CoV RNA polymerase.

Previous clinical trial data with zinc has demonstrated the potential to shorten the duration and intensity of the common cold, which is frequently caused by the rhinovirus and coronavirus families. Due to this potential benefit, physicians are questioning whether patients' COVID-19 treatment should include zinc supplementation. At this time, no professional societies have released statements supporting or refuting the use of zinc. A few clinical trials are underway regarding the role of zinc supplementation in COVID-19 treatment (NCT04342728) and prevention (NCT 04326725, NCT04335084). The dosing strategy currently outlined in the clinical trial investigating zinc use in COVID-19 treatment is 50 mg elemental zinc by mouth daily.

Zinc is available in intravenous, oral and intranasal formulations. Due to the risk of anosmia (ie, loss of smell) intranasal formulations are NOT recommended. There are multiple salt formulations and dosages are typically listed in milligrams of elemental zinc. Oral zinc supplements are commonly supplied over-the-counter as zinc gluconate. The most common side effects of zinc supplementation are nausea, vomiting, dyspepsia and abdominal pain. Zinc can bind to several medications, so administration should be separated from other enteral medications by three to four hours.

Trusted resources:

- Natural Medicines Comprehensive Database. Zinc. Last reviewed February 24, 2020. Accessed April 13, 2020. Available from: https://naturalmedicines.therapeuticresearch.com/
- Te Velthius AJ, et al. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog. 2010 Nov 4;6(11):e1001176. doi: 10.1371/journal.ppat.1001176.
- Coronarvirus Disease 2019 – Using ascorbic acid and zinc supplementation (COVIDAtoZ) research study. A randomized, open label single center study. Cleveland Clinic, Cleveland, Ohio. Available at: https://clinicaltrials.gov/ct2/show/NCT04342728?cond=zinc+and+covid&draw=2&rank=2
- Proflaxis for Healthcare Professionals Using Hydroxychloroquine Plus Vitamin Combining Vitamins C, D and Zinc During COVID-19 Pandemia: An Observational Study. Istinye University Medical School, Istanbul, Turkey. Available at: https://clinicaltrials.gov/ct2/show/NCT04326725?cond=zinc+and+covid&draw=2&rank=3

- An Open Label Phase II Pilot Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection. ProgenaBiome, Ventura, California. Available at: https://clinicaltrials.gov/ct2/show/NCT04335084?cond=zinc+and+covid&draw=2&rank=1

Q: What should I direct my patients with suspected COVID-19 infection to take for pain or fever?
A: A March 11, 2020 letter in the Lancet sparked media reports that ibuprofen may worsen symptoms of COVID-19. The theory is that because SARS-CoV2 attaches to target cells via the angiotensin-converting enzyme 2 (ACE2), medications that upregulate this enzyme, such as ACE-inhibitors, aldosterone receptor blockers, ibuprofen and thiazolidinediones, may increase the risk of developing severe COVID-19 infection. However, this was a theory published in a letter and not founded on any in vitro or in vivo studies. Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases and member of the White House Coronavirus Task Force, regarded the concerns as "urban legend," further emphasizing the lack of high-quality evidence that ibuprofen could worsen a course of coronavirus. The U.S. Food and Drug Administration (FDA) is investigating this theory further and published a statement on March 19, 2020 that they are not aware of evidence associated NSAIDs with worsening symptoms of COVID-19 infections. Also, the World Health Organization (WHO) made the following statement on their Twitter account on March 18, 2020: "Based on currently available information, WHO does not recommend against the use of ibuprofen."

At this time, no changes should be made in how you advise patients with confirmed or suspected COVID-19 infections to treat fever and myalgias. The usual considerations should be made for co-morbidities and safety profiles when deciding between ibuprofen/NSAIDs and acetaminophen.

Trusted Resources:
- FDA 3/19/2020 statement on the use of non-steroidal anti-inflammatory drugs for COVID-19: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19
- WHO statement on ibuprofen use for people with COVID-19: https://twitter.com/WHO/status/1240409217997189128

Q: Who can I contact at NM to discuss COVID-19 treatment-related questions?
A: NM Antimicrobial Stewardship Pharmacists are available to help with medication-related questions.
- NMH – Mike Postelnick or Brian Hoff at mposteln@nm.org or brian.hoff@nm.org
- Delnor - Jaime Borkowski at Jaime.borkowski@nm.org
- CDH - Radhika Polisetty at Radhika.polisetty@nm.org
- Lake Forest - Rishita Shah at Rishita.shah@nm.org
- Huntley, Woodstock and McHenry - Stephanie Chang at Stephanie.chang@nm.org

- Kish and Valley West – Kyle Johnicker at kyle.johnicker@nm.org

Continue to use COVID hotline (312.472.6843) for outpatient questions about your patients with COVID-19.

Q: What additional credible resources can I use for COVID-19-related questions?

- NMI COVID-19 page at: https://nmi.nmh.org/wcs/page/nm-coronavirus
- NM Physicians Forum at: https://physicianforum.nm.org/
- NM Antimicrobial Stewardship page at: https://asp.nm.org/
- State of Illinois COVID response: https://www2.illinois.gov/sites/coronavirus/Pages/default.aspx
- American Society of Health-Systems Pharmacists COVID-19 page https://www.ashp.org/Pharmacy-Practice/Resource-Centers/Coronavirus
- Illinois Pharmacist Association recommendations for medication dispensing: https://ilpa.memberclicks.net/assets/docs/Misc/IPhA%20Improper%20Medication%20Use%2020200322.pdf
- Illinois Department of Public Health Coronavirus Information: http://www.dph.illinois.gov/topics-services/diseases-and-conditions/diseases-a-z-list/coronavirus
- Illinois Department of Public Health Testing Decision Matrix: https://www.ichpnet.org/resources/covid-19/Clinical_Guidance_03142020.pdf
- CDC Coronavirus: https://www.cdc.gov/coronavirus/2019-ncov/index.html
- Departments of Public Health:
  - Illinois:
    - COVID Hotline: 800.889.3931
    - DPH.SICK@ILLINOIS.GOV
  - Chicago:
    - 312.746.4835
    - Coronavirus@chicago.gov
  - Cook County:
    - 708.633.4000
    - https://www.cookcountypublichealth.org/communicable-diseases/covid-19/